What Do Mutational Signatures Tell Us About Heritable Risk Factors and Targeted Therapy?

Colin Pritchard MD, PhD

University of Washington, Department of Lab Medicine

Brotman Baty Institute for Precision Medicine

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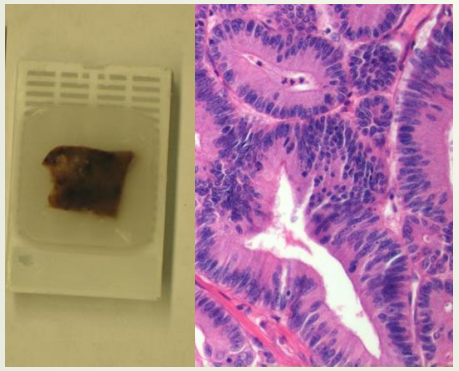
Disclosure Information

Consultant for Promega, AstraZeneca

Interplay

Tumor



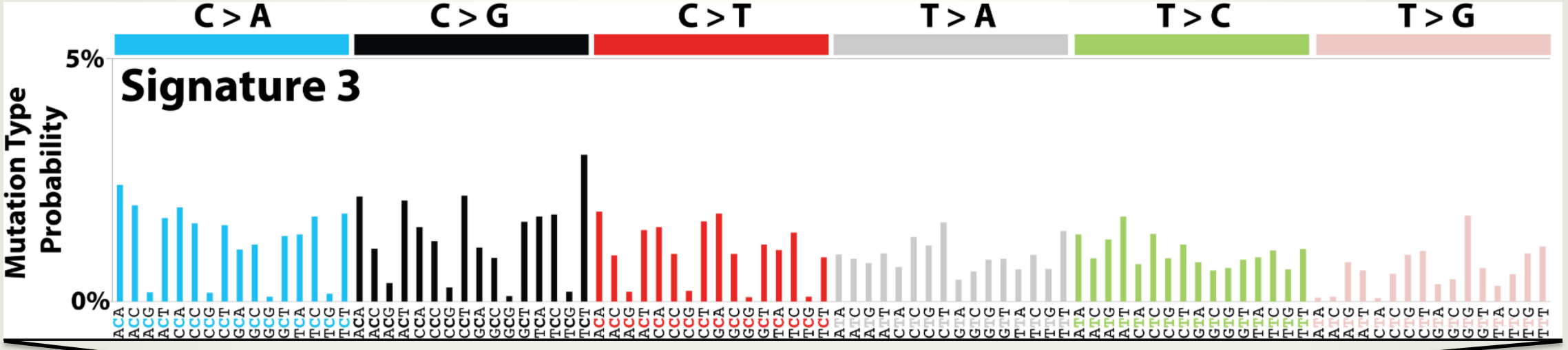
Germline

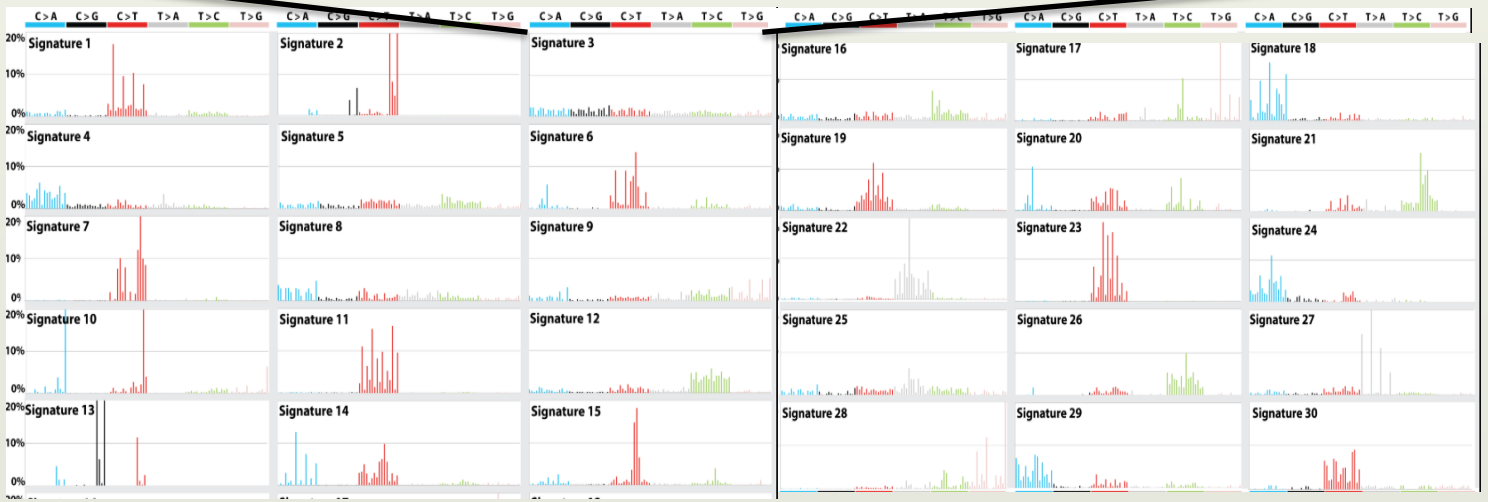
Targeted Therapy

Cancer Syndrome Screening

Variant Interpretation

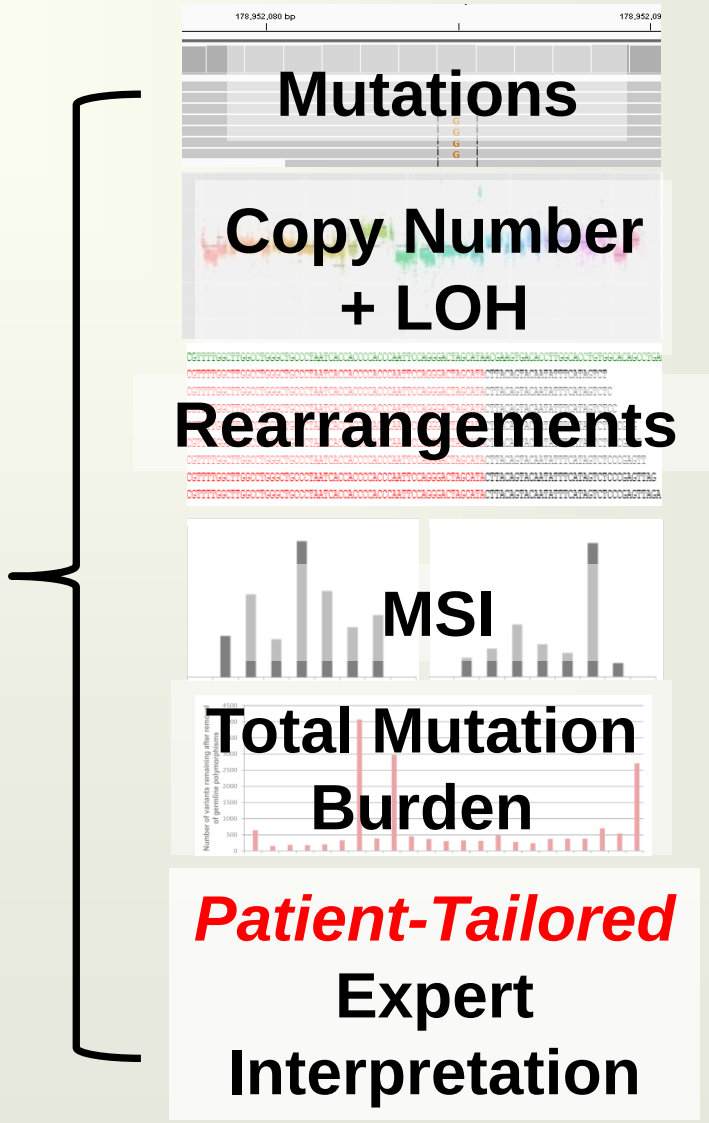
What Are Mutation Signatures?





Testing Approach at UW

- **Germline and tumor** paired sequencing
- DNA repair-focused NGS panel – **exons *AND* introns**



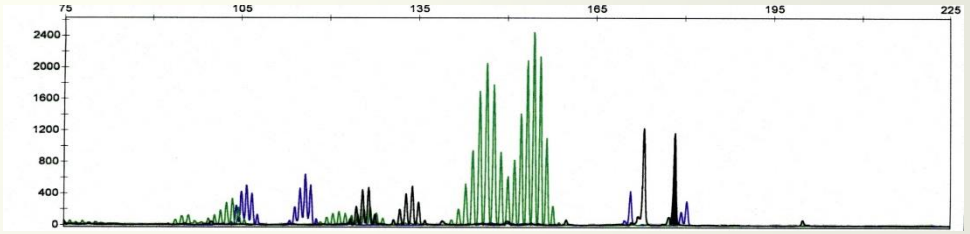
Actionable Mutation Signatures

Signature	Treatment Use	Germline Use
MSI	Immunotherapy	Lynch (HNPCC)
HRD (“BRCAness”)	PARPi, platinum	King (HBOC)
Transversion	Immunotherapy	*POLE/POLD1*
Ultra-hypermutation	Immunotherapy	CMMRD

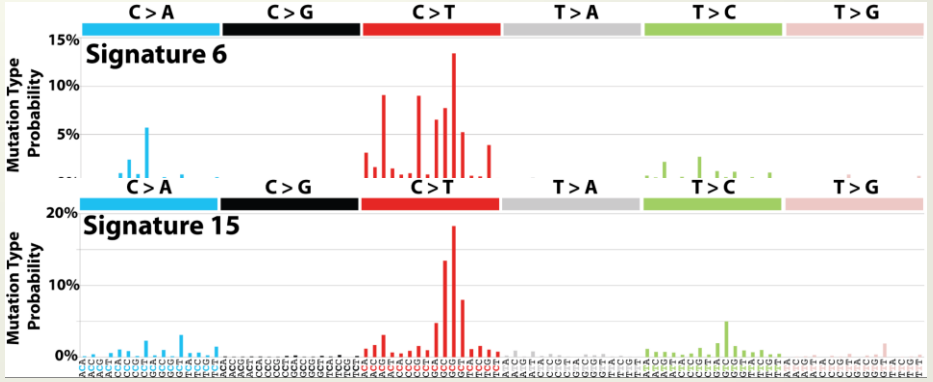
MSI: Microsatellite instability; HNPCC: Hereditary non-polyposis colorectal cancer; HRD: Homologous recombination repair deficiency; PARPi: Poly(ADP) ribose polymerase inhibitor; HBOC: Hereditary breast and ovarian cancer; CMMRD: Congenital mismatch repair deficiency

MSI/Mismatch Repair Deficiency (MMRd)

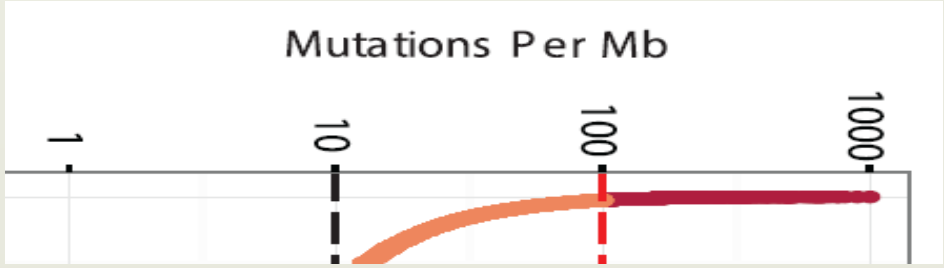
- **Microsatellite instability**



- **Single nucleotide mutation signatures**
  (COSMIC 6,15,20,26)

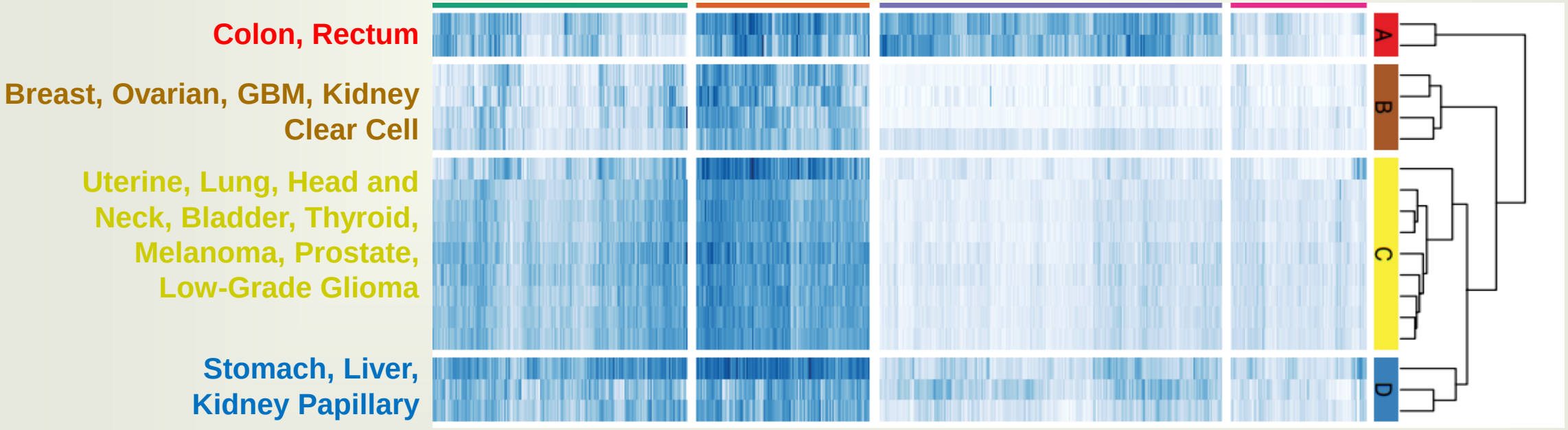


- **Hypermutation** (usually)



MMRd: Mismatch Repair deficiency

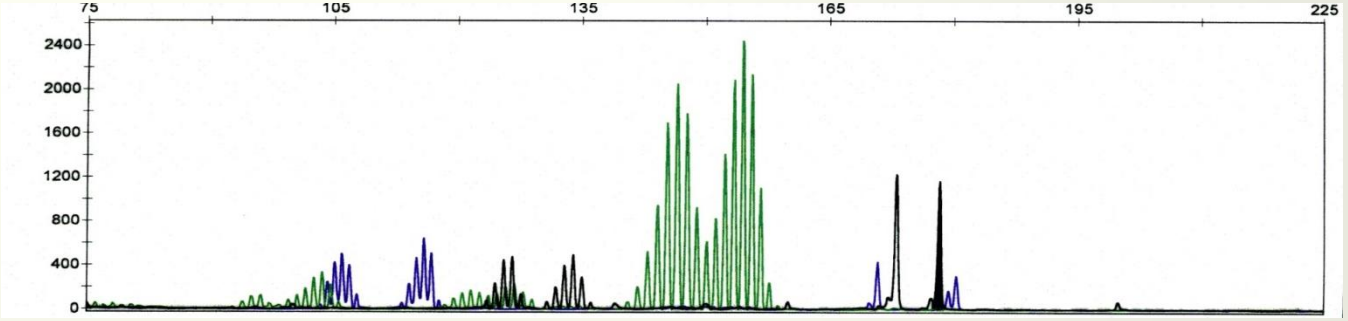
MSI Signatures Are Not The Same Between Cancer Types



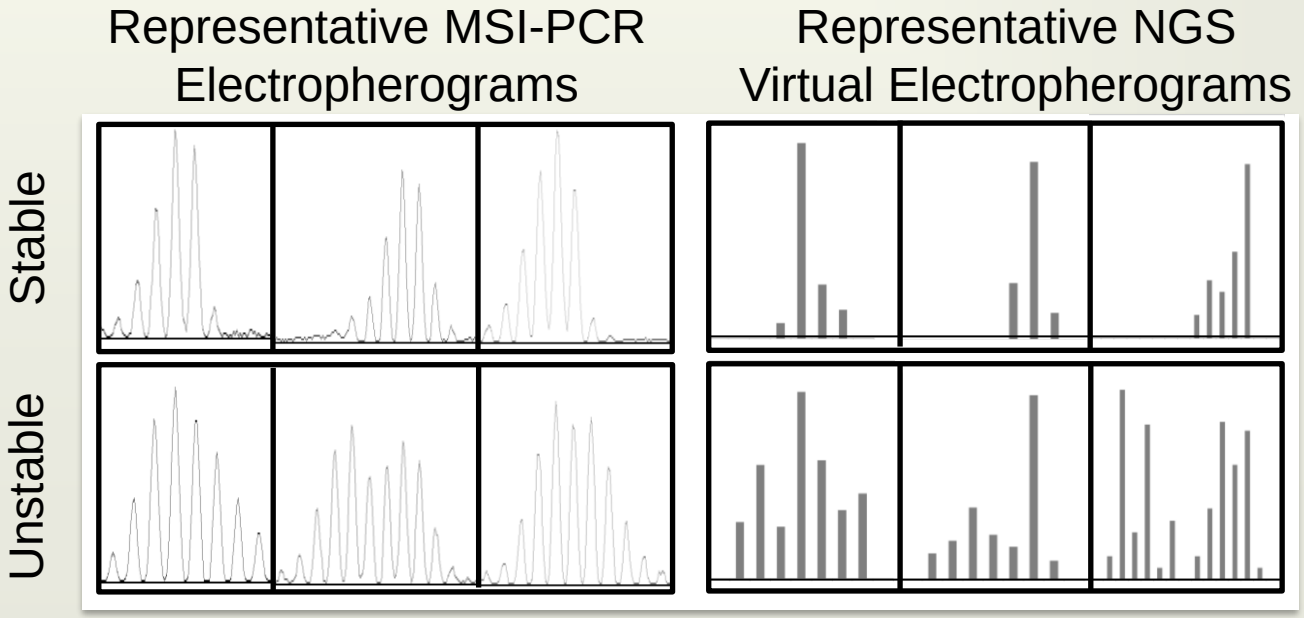
Hause et al. 2016 *Nat. Med*. PMID:27694933

How to MSI/MMRd Assays Work?

Capillary Electrophoresis
(Traditional Method)



Next Generation Sequencing
(Modern Method)



Salipante et al. (2014) *Clinical Chemistry* PMID:24987110

MSI/MMRd Clinical Utility

- **Checkpoint Blockade immunotherapy**

FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

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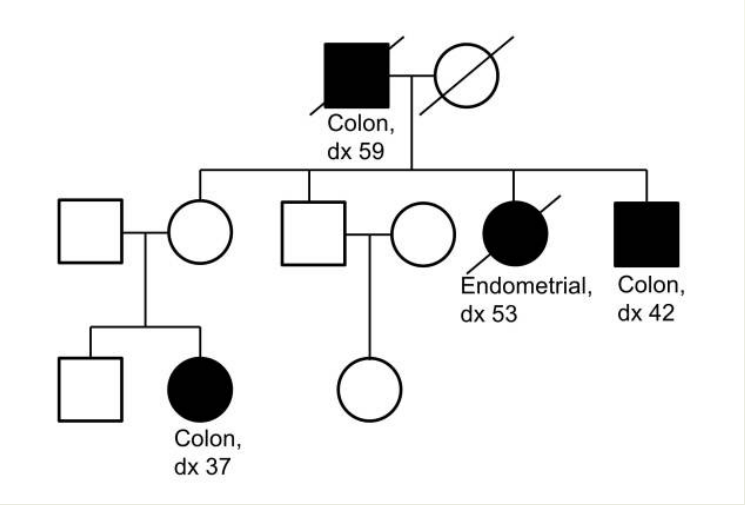
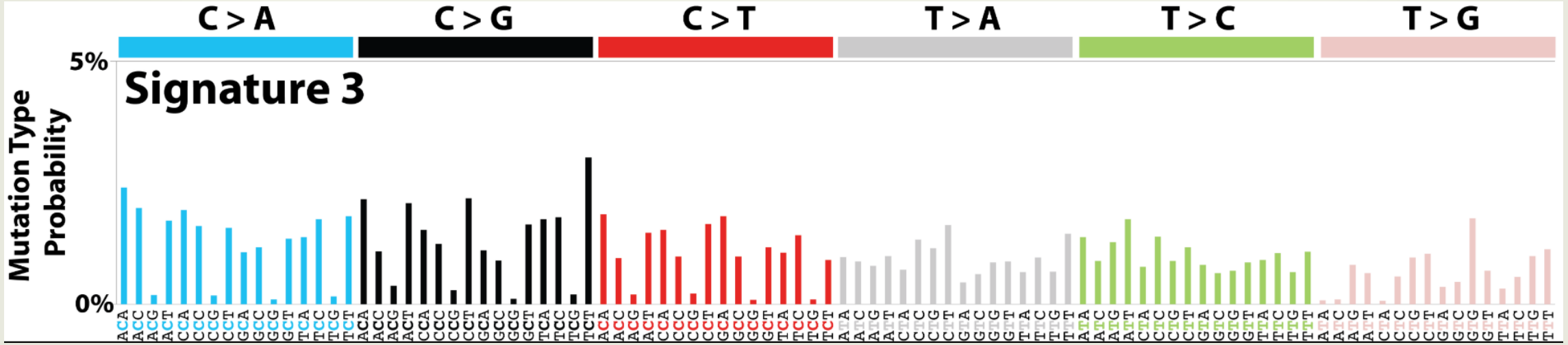
May 2017

- **Lynch screening**

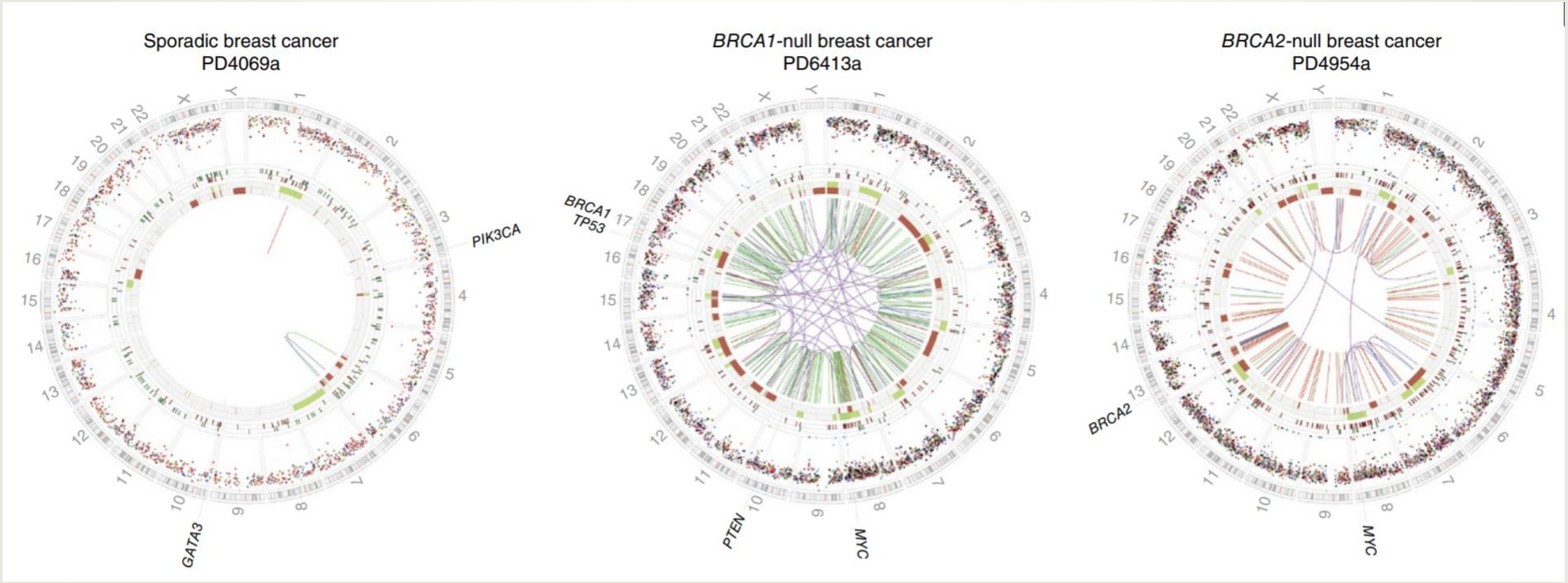


HRD Signature

- High level of loss of heterozygosity (LOH)
- Telomeric imbalance
- Deletions with microhomology (>3bp)
- Large Rearrangements



HRD Signature: ↑Rearrangements



Davies et al. (2017) *Nat. Genetics*

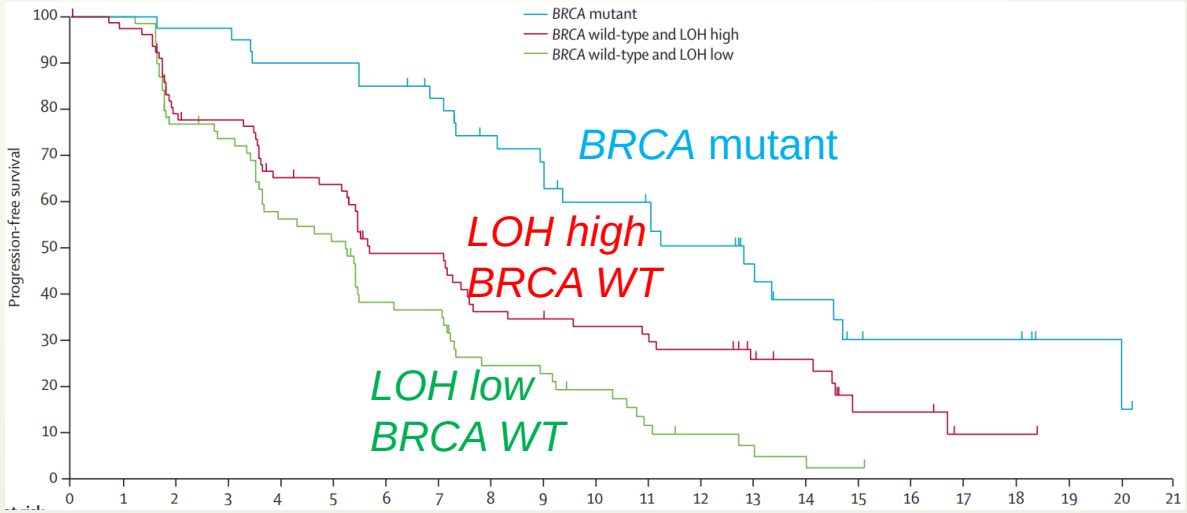
How Do HRD Score Assays Work?

- Level of LOH (high or low)
- “Genomic Instability Score”
  - LOH + Telomeric Imbalance + Large Rearrangements
- Newer Tests Have Additional Elements

LOH: Loss of Heterozygosity

HRD Clinical Utility

- **PARPi**
- **Platinum**



Adapted from Swisher et al. (2017) *Lancet Onc.*

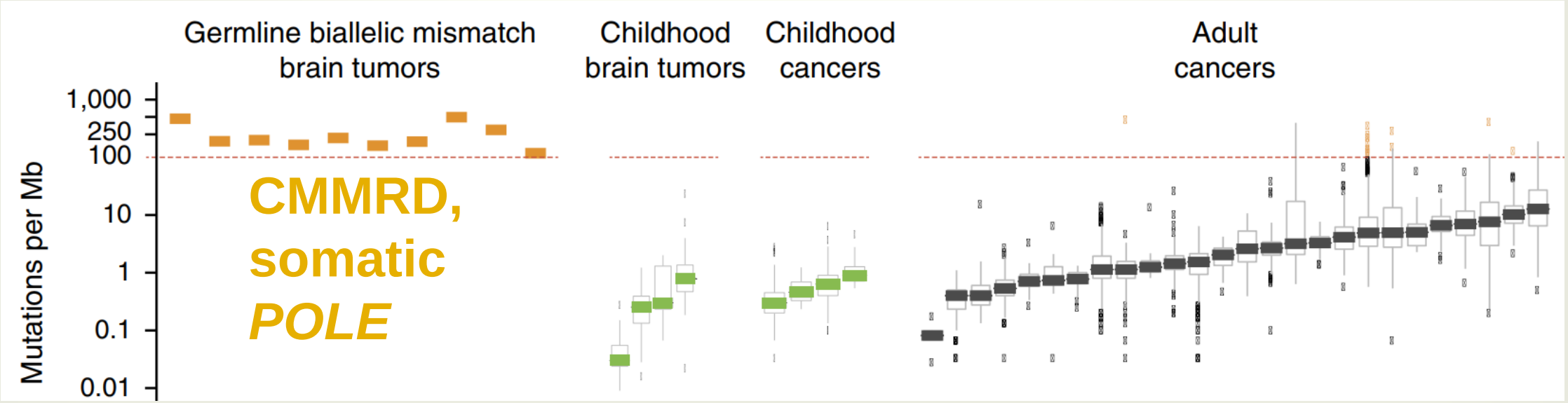
- **Variant Classification**

PARPi: Poly(ADP) Ribose Polymerase Inhibitor

POLE/POLD1

- Ultramutation (~>50 mutations/Mb)
- Transversions, C>A, G>T
- Immunotherapy responsiveness likely

Ultra-Hypermutation

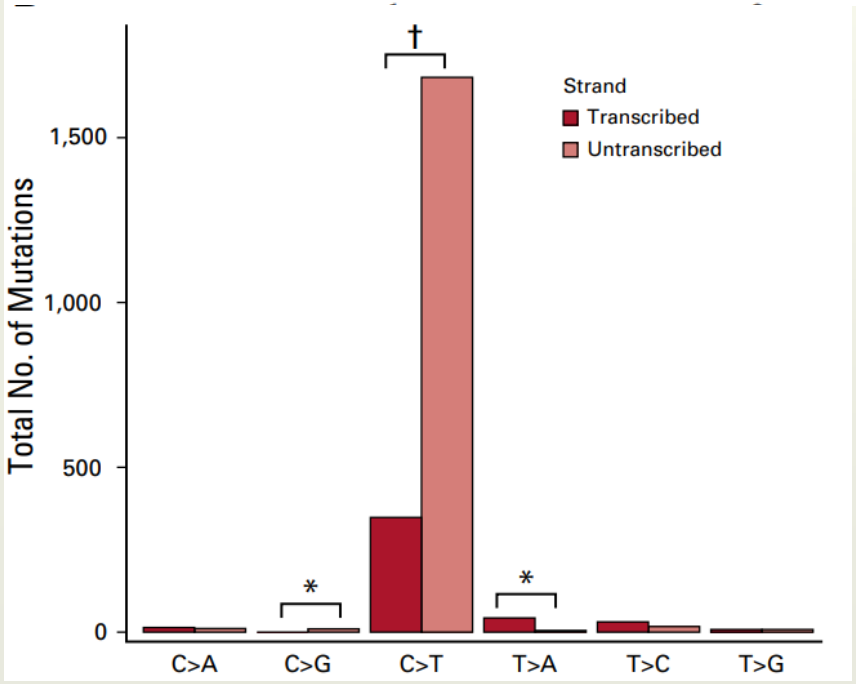


Shilen et al. 2015 *Nat. Genet*. PMID:25642631

Unusual Signatures

case report

Response to Pembrolizumab in a Patient With Xeroderma Pigmentosum and Advanced Squamous Cell Carcinoma



Nucleotide Excision Repair Deficiency Signature

Tumor in child with bi-allelic germline *XPC* mutation

Steineck et al. (2019) *JCO Precision Oncology*

Tumor Mutation Signatures Can Inform Germline Variant Classification

- Best established with MMR VUS, looking for MSI
- Increasingly used *BRCA1/2* VUS, looking for HRD
- *POLE/POLD1* VUS, looking for transversion signature

VUS= variant of uncertain significance, MMR= mismatch repair, HRD= homologous recombination DNA repair deficiency

Summary

- Tumor **mutation signatures** increasingly **used to guide cancer treatment**
- Mutation **signatures can help in a germline** cancer predisposition **workup**
- Mutation signatures **can assist with variant classification**

Thank You!